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SYNTHESIS AND ABSOLUTE CONFIGURATION OF TWO DIASTEREOISOMERIC (1*R*, 2*S*, 3*R*)-AND (1*S*, 2*S*, 3*R*)-2-AMINO-1-(2-FURYL)-1, 3-BUTANDIOLS

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Abstract—The synthesis of (1*R*, 2*S*, 3*R*)-and (1*S*, 2*S*, 3*R*)-2-(N-benzoylamino)-1-(2-furyl)-1, 3-butandiols (**15**) and (**16**) from D-threonine is described. The assignment of absolute configuration of the newly formed asymmetric center at C-1 was based on the ^{1}H-NMR spectra of O-isopropylidene derivatives **17** and **18**.

Of particular interest amongst higher carbon sugars is 6-amino-6,8-dideoxy-D-erythro-D-galactooctose (lincosamine) **1**, a component of the antibiotic lincomycin which is active against a wide spectrum of gram-positive bacteria.[1] Consequently the synthesis of lincosamine and its analogoues has received much attention.

A general method for the stereoselective synthesis of monosaccharides from furan compounds[2] has provided a possible route to higher-carbon sugars (i.e. heptoses, octoses, nonoses, etc) with a defined relative configuration of the side chain and pyranose ring. It has also been demonstrated that the optical purity of the starting furan derivative is retained in the final product,[3] hence the applicability of this method to the synthesis of enantiomerically pure sugars of specified absolute configuration.

Substituted furans of type **2** are required for the synthesis of 6-amino-6,8-dideoxyoctoses. In this report the synthesis of the two enantiomerically pure diastereoisomers of **2**, with the absolute configurations (1*R*, 2*S*, 3*R*) and (1*S*, 2*S*, 3*R*), is described.

RESULTS AND DISCUSSION

Our approach utilizes a known reaction of lithium salts of carboxylic acids with organolithium compounds yielding the respective ketones.[4] Reaction of furyllithium with salts of appropriate carboxylic acids should lead in theory to furan compounds with a side chain of any length and functionalization, e.g. we have found that lithium 2, 3-O-isopropylidene-2, 3-dihydroxybutyrate (**3**) reacted with furyllithium to give an excellent yield of ketone **4**, which, on reduction of the CO group, yielded two epimeric 1-(2-furyl)-1, 2, 3-butantriols **5**; these being substrates for the synthesis of 8-deoxyoctoses.[5]

D-Threonine (**6**), an amino acid readily available in an optically pure state, has been used as starting material in the present synthesis. The OH and amino groups of D-threonine have been protected by conversion,[6] into the lithium salt of Δ-2-oxazoline (**8**). This reaction sequence proceeds with two inversions, one at each asymmetric C atom, and hence the oxazoline **8** obtained has the L-threo configuration.

Reaction of lithium salt **8** with furyllithium in ether, THF or a THF–ether mixture, either at low temperature or under reflux, for 4–20 hr, afforded the expected ketone **9** (Scheme) in only about 30% yield. Structure **9** was evident from analytical and spectral data. In the IR spectrum bands at 1683 and 1643 cm^{-1} confirmed the presence of a conjugated CO and C=N groups respectively. In the ^{1}H-NMR spectrum signals, corresponding to all the protons present in **9** (Experimental), have been assigned.

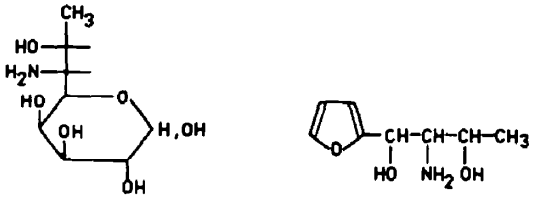


Fig. 1.

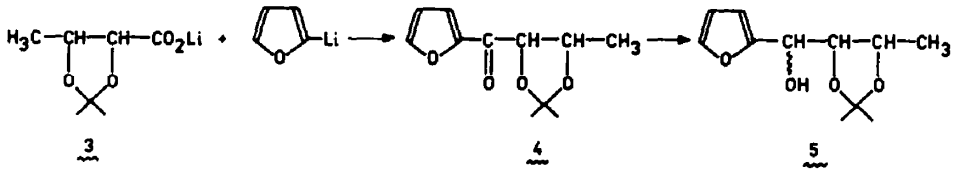


Fig. 2.

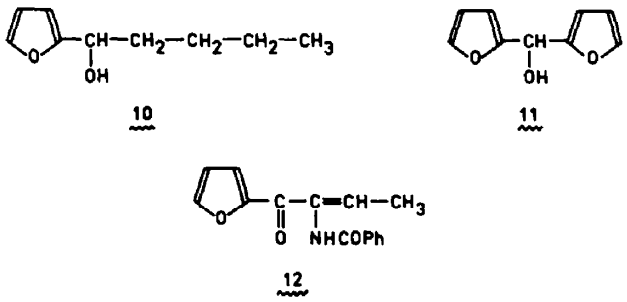
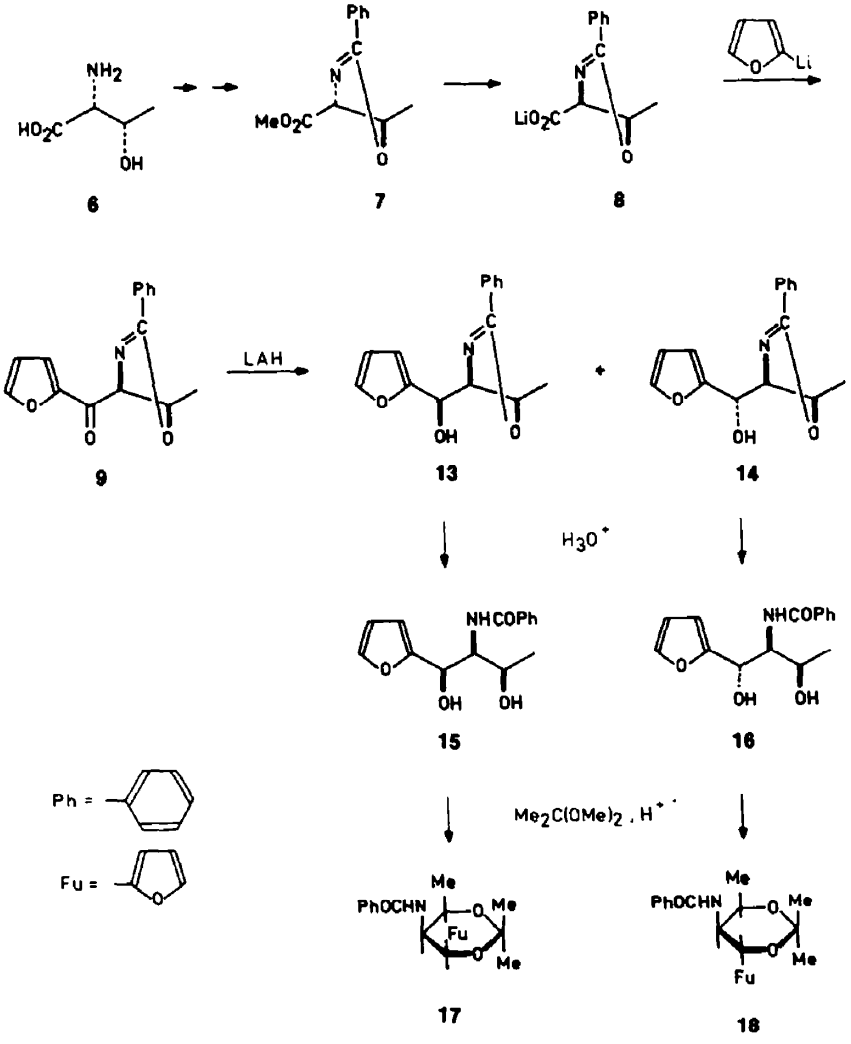


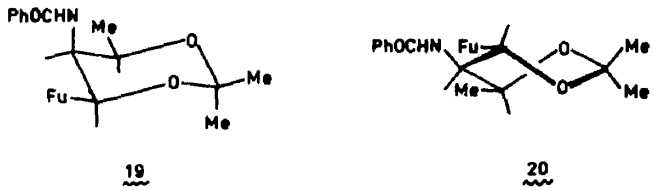
Fig. 3.

Side reactions are responsible for the low yield of **9**. Depending on the reaction conditions, the formation of varying amounts of different side products have been observed by tlc. Three of these products have been separated by column chromatography and the following structures, **10**, **11** and **12**, have been deduced on the basis of the ^{1}H-NMR spectra (Experimental) (Fig. 3).

Treatment of ketone **9** with LAH yielded in the ratio 3:1 two products **13** and **14** which were separated by column chromatography. The IR spectra showed that only the keto group had been reduced leaving the oxazoline C=N unchanged (1640 and 1638 cm^{-1}). In both carbinols **13** and **14** the oxazoline rings were cleaved by acid hydrolysis to give the N-benzoyl derivatives **15** and **16**, respectively.

The configuration at C-2 (*S*) and C-3 (*R*) in compounds **15** and **16** was evident from the method of preparation. In order to determine the configuration of the OH group at C-1, compounds **15** and **16** have been converted into the isopropylidene derivatives **17** and **18**, respectively, by treatment with 2,2-dimethoxypropane. The ^{1}H-NMR spectra allowed the assignment of the configuration at C-1 on the basis of the following argument: It is known that in case of 2,2-dimethyl-1,3-dioxanes substituted at





19 20

Fig. 4.

C-4 and C-6, the isomers possesing substituents in these positions in *cis* relationship usually occur in the chair conformation with both substituents occupying an equatorial position. On the other hand dioxanes in which the substituents at C-4 and C-6 are *trans* adopt the twist-boat conformation[7]. This is because in either of the two chair forms there are strong *syn*-diaxial interactions between the C-2 Me group and the substituent at C-4 or C-6. Therefore we could predict that isomer **17** with the (1*R*) configuration occurs in the chair conformation **19**, whereas for the (1*S*) isomer **18** the twist-boat conformation prevails (Fig. 4).

In the ^{1}H-NMR spectrum of the isopropylidene derivative of the major reduction product, coupling constants $J_{1,2} = 1.3$ and $J_{2,3} = 1.7$ Hz were found. These values were taken as evidence of the chair conformation **19** and consequently the absolute configuration (1*R*, 2*S*, 3*R*) for the major reduction product **13**. Therefore the configuration of the minor product **14** must be (1*S*, 2*S*, 3*R*). The predominance of the twist-boat conformation **20** of its isopropylidene derivative **18** is confirmed by the coupling constants $J_{1,2} = 6.1$ and $J_{2,3} = 3.7$ Hz.

This reported synthesis of the 2 - amino - 1 - (2 - furyl) - 1, 3 - butandiols from D-threonine has enabled us to make an unequivocal assignment of the absolute configuration of the two aminodiols **15** and **16**. Unfortunately it has limited preparative value because of the low yield obtained in the condensation step.

EXPERIMENTAL

General. M.ps were taken on a Kofler hot stage apparatus and are uncorrected. IR spectra (KBr discs) and UV spectra were recorded on a Unicam SP-200 spectrometer and a Unicam SP-500 spectrometer, respectively. Optical rotations were measured with a Perkin Elmer 141 polarimeter. ^{1}H-NMR spectra were obtained using a Jeol JNM-4H-100 or Varian EM 360 (60 MHz) spectrometers. Silica gel G (Merck) was used for tlc. The term "dried" signifies the use of anhyd $MgSO_4$. All reactions and chromatographic separations were monitored in tlc.

Methyl (2*R*, 3*R*)-2, 3(N, O-benzylidyne)-2-amino-3-hydroxybutyrate (**7**), m.p. 72–74°C, $[\alpha]_D$ − 67.5° (*c* 2.8, EtOH) was obtained from D-threonine (**6**) by following the literature[6] method.

Lithium (2S, 3R) - 2, 3 - (N, O-*benzylidyne*) - 2 - *amino* - 3 - *hydroxybutyrate* (**8**). A soln of **7** (6.58 g, 0.03 mol) in EtOH (32 mL) was added to Li (0.22 g, 0.0314 mol) in EtOH (32 mL). After 5 min at room temp water (64 mL) was added and the mixture refluxed for 20 min. The solvents were removed under reduced pressure and the residue dried at 100° *in vacuo* to yield **8** (6.55 g), $[\alpha]_D$ +96° (*c* 1.28, EtOH:H_2O 1:1), IR: 1640, 1420 (CO_2^-); 1580, 1500 (Ph) cm^{-1}; ^{1}H-NMR (D_2O, δ): 8.15–7.93 (m, 2H) and 7.76–7.50 (m, 3H, phenyl); 5.04 (dq, 1H, $J_{2,3} = 7.2$, $J_{3,4} = 6.3$ Hz, H-3); 4.38 (d, 1H, H-2); 1.53 (d, 3H, 4-CH_3).

(2S, 3R) - 2, 3 - (N, O-*Benzylidyne*) - 2 - *amino* - 1 - (2 - *furyl*) - 3 - *hydroxy* - 1 - *butanon* (**9**). Furan (2.5 g, 0.035 mol) was added to a cooled (− 10°) THF soln of BuLi prepared from BuCl (2.3 g, 0.025 mol) and Li (0.4 g). The mixture was allowed to reach room temp and stirred for 1 hr and the resultant soln was added dropwise at 0° under N_2, to a suspension of **8** (4.22 g, 0.02 mol) in anhyd ether (50 mL). After 2 hr at 0° the mixture was allowed to reach room temp (1 hr), then poured into cold water (50 mL) and extracted three times with ether. The combined extracts were dried and evaporated to give a semisolid (3.2 g). The solid was removed by filtration to give **9** (1.08 g, 21.2%) and the filtrate (dark yellow oil) was chromatographed on silica (25 g). Elution with ligroin–ether (95:5) afforded a second crop of **9** (0.43 g, 8.4%), m.p. 69.5–71°; $[\alpha]_D$ +249.5° (*c* 0.6, $CHCl_3$); IR: 1683 (C=O); 1643 (C=N); 1582, 1570 (Ph); 1501, 920 (Fu) cm^{-1}; ^{1}H-NMR ($CDCl_2$, δ): 7.96 (m, 2H) and 7.40 (m, 3H, phenyl); 7.63 (m, 2H) and 6.55 (dd, 1H, J = 2.5 and 3.7 Hz, H-β furan); 5.22 (dq, 1H, $J_{2,3} = 6.8$, $J_{3,4} = 6.2$ Hz, H-3); 4.95 (d, 1H, H-2); 1.53 (d, 3H, 4-CH_3); UV (EtOH): 274.5 (21037); 229 (12088) nm; (Found: C, 70.6; H, 5.1; N, 5.5; Calc. for $C_{15}H_{13}NO_3$: C, 70.6; H, 5.1; N, 5.4%).

Further elution of the column gave:

1-(2-*Furyl*)-1-*pentanol* (**10**). (0.2 g; 6.5% yield); ^{1}H-NMR ($CDCl_3$, δ): 7.46 (m, 1H) and 6.45–6.25 (m, 2H, furan); 4.72 (t, 1H, J = 7 Hz, H-1); 2.41 (bs, 1H, OH); 1.76–1.66 (m, 2H, H-2, H-2'); 1.53–1.17 (m, 4H, H-3, H-3', H-4, H-4'); 1.08–0.8 (m, 3H, 5-CH_3).

1-(2-*Furyl*) *furfuryl alcohol* (**11**). (0.35 g, 10.6% yield); ^{1}H-NMR ($CDCl_3$, δ): 7.46 (m, 2H) and 6.36 (m, 4H, furan); 5.8 (s, 1H, H-1); 3.85 (bs, 1H, OH).

2 - (N - *Benzoylamino*) - 1 - (2 - *furyl*) - 2 - *buten* - 1 - *one* (**12**). (0.11 g, 2.1% yield); ^{1}H-NMR ($CDCl_3$, δ): 8.58 (bs, 1H, NH); 8.09–7.4 (m, 7H, aromatic); 6.89 (q, 1H, J = 7 Hz, H-3); 6.63 (dd, 1H, J = 2.5 and 4 Hz, H-β furan); 1.97 (d, 3H, 4-CH_3).

(1*R*, 2*S*, 3*R*) *and* (1S, 2S, 3R) - 2, 3 - (N, O - *Benzylidyne*) - 2 - *amino* - 1 - (2-*furyl*) - 1, 3 - *butandiol* (**13** *and* **14**)

Compound **9** (2.6 g, 0.01 mol) in anhyd ether (150 mL) was reduced at 0° with LAH (0.5 g). After hydrolysis (H_2O, 2N NaOH) the ether soln was dried, evaporated to dryness and the residue chromatographed on silica (60 g). Elution with ligroin–ether (95:5) gave:

(a) Compound **14** (0.57 g, 21.7%): m.p. 118.5–119.5°C; $[\alpha]_D$ −27.16° (*c*1, $CHCl_3$); IR: 3180 (OH); 1638 (C=N); 1605, 1585 (Ph); 1503 (Fu) cm^{-1}; ^{1}H-NMR ($CDCl_3$, δ): 7.75 (m, 2H); 7.48–7.28 (m, 4H) and 6.34 (m, 2H, aromatic); 5.27 (d, 1H, $J_{1,2} = 2.9$ Hz, H-1); 5.22 (bs, 1H, OH); 4.85 (dq, 1H, $J_{2,3} = 7.9$, $J_{3,4} = 6.4$ Hz, H-3); 4.16 (dd, 1H, H-1); 1.16 (d, 3H, 4-CH_3); (Found: C, 69.9; H, 5.8; N, 5.3; Calc. for $C_{15}H_{15}NO_3$: C, 70.0; H, 5.9; N, 5.4%).

(b) Compound **13** (1.87 g, 72.7%): m.p. 113–113.5°; $[\alpha]_D$ + 50.46° (*c*1, $CHCl_3$); IR: 3150 (OH); 1640 (C=N); 1603, 1580 (Ph); 1501, 920 (Fu) cm^{-1}; ^{1}H-NMR ($CDCl_3$, δ): 7.96 (m, 2H), 7.43 (m, 4H) and 6.40 (m, 2H, aromatic); 4.58 (d, 1H, $J_{1,2} = 7.5$ Hz, H-1); 4.50 (dq, 1H, $J_{2,3} = 7.5$, $J_{3,4} = 6.2$ Hz, H-3); 4.19 (dd, 1H, H-2); 3.91 (bs, 1H, OH); 1.24 (d, 3H, 4-CH_3); (Found: C, 70.0; H, 6.0; N, 5.6; Calc. for $C_{15}H_{15}NO_3$: C, 70.0; H, 5.9; N, 5.4%).

(1R, 2S, 3R) - 2 - (N-*Benzoylamino*) - 1 - (2-*furyl*) - 1, 3 - *butandiol* (**15**)

To a soln of **13** (1.1 g, 4 mmol) in THF (5 mL) was added 5N HCl (1 mL). After 4.5 hr the mixture was brought to pH 9 with 2N NaOH and extracted with chloroform (3·200 mL). The combined extracts were dried and evaporated yielding crude **15** (1.1 g, 93.5%), which was purified by crystalization from ether-EtOAc, m.p. 151–153°; $[\alpha]_D$ +36.7° (*c* 0.8, $CHCl_3$); IR: 3360 (OH); 1635 (C=O); 1580, 1550 (Ph) cm^{-1}; (Found: C, 65.5; H, 6.3; N, 5.2; Calc for $C_{15}H_{17}NO_4$: C, 65,4; H, 6.2; N, 5.1%).

(1S, 2S, 3R) - (N-*Benzoylamino*) - 1 - (2-furyl) - 1, 3 - *butandiol* (**16**)

Using the preceding procedure, **14** was converted to **16** (60% conversion, 93% yield), m.p. 117–118°; $[\alpha]_D$ + 5.03 (*c* 0.9, $CHCl_3$);

IR: 3400 (OH); 1615 (C=O); 1580, 1540, (Ph) cm^{-1}; (Found: C, 65.4; H, 6.2; N, 5.1; Calc. for $C_{15}H_{17}NO_4$: C, 65.4; H, 6.2; N, 5.1%).

(1R, 2S, 3R) - 1, 3 - O - *Isopropylidene* - 2 - (N-*benzoylamino*) - 1, 3 - *butandiol* (**17**).

To a soln of **15** (0.3 g, 1.1 mmol) in dimethoxypropane (5 mL) was added *p*-TsOH (10 mg) and the mixture was left overnight, then neutralized with a drop of triethylamine. Solvent was removed by evaporation and the residue partitioned between ether and water. The ether phase was washed with water, dried and evaporated to give **17** (0.32 g, 95.7%), m.p. 142–144°; $[\alpha]_D$ +29.08° (*c*1, $CHCl_3$); IR: 3510 (NH); 1670 (C=O); 1585, 1525 (Ph) cm^{-1}; ^{1}H-NMR ($CDCl_3$, δ): 7.75–7.65 (m, 2H) and 7.16–6.96 (m, 4H, aromatic); 6.65 (bd, 1H, $J_{2,NH}$ = 10.0 Hz, NH); 6.35 (d, 1H, J = 3.7 Hz, furan); 6.0 (dd, 1H, J = 3.7 and 2.5 Hz, furan); 4.93 (d, 1H, $J_{1,2}$ = 1.3 Hz, H-1); 4.40 (dxdxd, 1H, $J_{2,3}$ = 1.7 Hz, H-2); 3.80 (dq, 1H, $J_{3,4}$ = 6.2 Hz, H-3); 1.44 (s, 3H, CH_3); 1.27 (s, 3H, CH_3); 1.15 (d, 3H, 4-CH_3); (Found: C, 68.4; H, 6.7; N, 4.3; Calc. for $C_{18}H_{21}NO_4$: C, 68.5; H, 6.7; N, 4.4%).

(1S, 2S, 3R) - 1, 3 - O - *Isopropylidene* - 2 - (*N-benzoylamino*) - 1, 3 - *butandiol* (**18**)

Using the preceding procedure, **16** was converted to **18** (95% yield), m.p. 111–114°; $[\alpha]_D$ + 108.1° (*c*1, $CHCl_3$); IR: 3340 (NH); 1645 (C=O); 1585, 1550 (Ph) cm^{-1}; ^{1}H-NMR ($CDCl_3$, δ): 7.74-7.62 (m, 2H) and 7.16–6.98 (m, 4H, aromatic); 6.81 (bd, 1H, $J_{2,NH}$ = 9.95 Hz, NH); 6.37 (d, 1H, J = 3.7 Hz, furan); 6.05 (dd, 1H, J = 3.7 and 2.5 Hz, furan); 5.01 (dxdxd, 1H $J_{1,2}$ = 6.1, $J_{2,3}$ = 3.7 Hz, H-2); 4.86 (d, 1H, H-1); 4.30 (dq, 1H, $J_{3,4}$ = 6.2 Hz, H-3); 1.45 (s, 3H, CH_3); 1.23 (s, 3H, CH_3); 1.18 (d, 3H, 4-CH_3); (Found: C, 68.5; H, 6.8; N, 4.3; Calc. for $C_{18}H_{21}NO_4$: C, 68.5; H, 6.7; N, 4.4%).

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